REMARKS/ARGUMENTS

Claims 44-107 are pending in this application. The elected Group III claims, i.e., nos. 46, 52, 53, 59, 65, 70 and 90, are rejected. The non-elected claims, namely nos. 44, 45, 47-51, 54-58, 60-64, 66-69, 71-89 and 91-107, have been withdrawn from further consideration by the Examiner.

Provided with this response is a "Second Declaration of Prof. Dr. Hermann Haller Under 37 C.F.R. §1.132". The declaration presents evidence which supports the non-obviousness of applicants' claims presently under examination. The Examiner is respectfully requested to reconsider and withdraw the rejection of applicants' claims under 35 U.S.C. §103(a) based on the evidence provided in the 1.132 declaration, taken in conjunction with the remarks set forth below.

Claim Rejections Under 35 U.S.C. §103

The Examiner continues to maintain the rejection of claims 46, 52, 53, 59, 65, 70 and 90 under 35 U.S.C. §103. The claims are rejected over the previously cited combination of four references, namely Fatouros, M.S., et al., *Eur. J. Surg.* (1999), Krussel, J.S., et al., *Mol. Hum. Reprod. (2001)*, EP 0613683 (Amgen) and U.S. Patent No. 6,274,158 (Zaharia Czeizler), taken in combination with a newly cited reference, i.e., U.S. Patent No. 6,784,154 of Westenfelder The rejection is respectfully traversed.

The features which applicants submit distinguish their claimed method from the previously cited references have been extensively discussed in the last two responses filed in regard to this application, i.e., on November 26, 2007 and May 7, 2008. Those remarks are specifically incorporated by reference into this response. Nevertheless, for the sake of clarity, a brief non-limiting summary of the previous arguments, along with an argument concerning how the claimed method distinguishes over the newly-cited Westenfelder reference, is being provided in order to place certain additional arguments presented herein in their proper context.

As applicants have previously pointed out, the prior art discloses values of EPO that are not simply different in amount from those used in the presently claimed method, they also differ in the effect in the patient's body caused due to the administration of the significantly higher

levels of EPO taught for use therein. That is, the teachings contained in the subject references represent a difference in kind, not just in amount.

The Fatouros reference, for example, discloses to administer 55 IU/kg/day for 22 days, which amounts to 22 x 500 = 11,000 IU/kg/22 days or approximately 3,500 IU/kg/week. In contrast, the claims to the applicants' method recite a weekly dosage of 1 to 90 IU EPO/kg of body weight.

Turning, next, to the Zaharia Czeizler U.S. '158 patent, as previously argued applicants submit that this reference also discloses the use of significantly higher dosages than that which is claimed by applicants. The patentee teaches a first or initial treatment with EPO using dosages such as 5,000 IU/EPO/day (Example 1), or 3 times per week (see Example 2), or 4,000 IU three times per week (Example 3). Assuming an average patient body weight of 75 kg, the subject patent is thus teaching to use significantly higher EPO dosage levels than that recited by applicants. Furthermore, as previously pointed out in applicants' earlier filed response, in addition to the initial EPO treatments noted above, the reference also teaches that patients subsequently received additional treatments with EPO, thus further increasing the amount of EPO administered.

The next reference, i.e., the Amgen European patent publication (EP 0 613 683) also teaches to use (for preparing a pharmaceutical composition), significantly higher dosages of EPO than are contemplated by applicants for use in their presently claimed method. See, for example, the disclosure at p. 5, lines 9-10 (500, 1500 and 4500 IU/kg/EPO) and p. 8, lines 33-35 (500 IU/kg/EPO).

Applicants thus construe the combined teachings of the above-discussed references as being directed towards the use of dosages which are significantly larger than those recited in the presently pending claims.

The Krussel et al. reference is cited due to its teaching to use VEGF to stimulate endothelial progenitor cells and induce angiogenesis, which the Examiner has interpreted as falling within the scope of "wound healing".

Furthermore, as indicated above and as applicants have previously argued, the differences between the range of dosages taught for use in the prior art versus those recited in the present

claims have a marked impact on the effect of the EPO so administered. This represents a difference not only in amount, but also in kind (see below).

As would be well known to one having an ordinary level of skill in this art, the administration of high dosage levels of EPO, i.e, of the sort taught in the prior art, results in significantly different effects to the subject to whom the composition is administered than the different 'class' of lower dose as taught for use by applicants.

For example, in the case of the '158 Zaharia Czeizler U.S. patent, as demonstrated by the Examples set forth therein, the EPO dosages used significantly increased the hemoglobin values in the blood of the patients (see, e.g., col. 4, line 44, col. 5, lines 24-25, col. 7, line 28, etc.). This is in clear contrast to applicants' presently claimed invention wherein the aim is to heal wounds and to do so without affecting the hemoglobin value, i.e., referred to as the hematocrit value. In this regard the applicants respectfully direct the Examiner's attention to p. 27 of their application (line 9, et seq.) which teaches that the doses provided according to the present invention are subpolycythemic doses, i.e., doses which do not lead to erythrocytosis (with hematocrit values >50%) which means that the amount of hemoglobin in the system is not significantly increased. Further in contrast to the present invention, moreover, the reference teaches at col. 5, line 56 to use even higher doses of EPO at more frequent transfusions to achieve the desired result which, as noted above, is not the result sought by the use of applicants' claimed method.

Additionally, in reviewing the teaching of EP 0613683 relied upon (in combination with the other cited references to reject the present claims), it is evident from, e.g., Fig. 4 of the subject reference that at least one aim of the method described therein is to have a significant effect on the red blood cell count - that is, administration of dosages of the level taught by EP 0613683 and the other cited art significantly increases the hematocrit value of a subject's blood. This significant increase, therefore, correspondingly has an important effect on the subject's blood pressure, as well as producing a number of additional physical manifestations which are well known in this field of art.

In contrast, as indicated above p. 27 of applicants' specification teaches the dosages used in the presently claimed method are subpolycythemic doses which do not lead to erythrocytosis with hematocrit values of more than 50%. It is for this reason, therefore, that the dosages used in

applicants' claimed method are 'very small amounts' which are significantly below the dosages taught for use in the prior art.

It is additionally evident from Fig. 4 of the Amgen Ref. No. 0 613 683 that at least one aim of the method taught by the subject reference is to significantly increase the hematocrit value of a patient. It can be seen, based on the discussion above, that such an effect as that sought by the subject reference is entirely undesirable in the case of the presently claimed method.

Further to the summary provided above, as noted the Examiner in the present Office Action has added a newly-cited reference to the combination relied upon to reject the claims, namely Westenfelder U.S. Patent No. 6,784,154. According to the Office Action the subject reference contains a teaching that defines subpolycythemic erythropoietin dosis and ranges as being about 250-350 U/kg of body weight. Applicants have closely reviewed this reference and note that it discloses subpolycythemic doses of EPO for the treatment of acute renal failure. However, the doses disclosed (see, for example, col. 6 line 45 to col. 7 line 17), are still considerably higher than the dose recited for use in the claims presently under examination. This is particularly true considering that the 250 to 350 units per kilogram body weight mentioned therein are obviously applied several times per week - this is evident from, e.g., col. 7, first full paragraph, and Example 5.

Additionally, the reference does not disclose an effect specifically and exclusively linked to a wound healing process. It is, moreover, apparent from the context found in the application that the patentee prefers the use of the given, i.e., relatively low, subpolycythemic dosage of 250 to 350 units/kg of body weight over the conventionally used higher doses of EPO (i.e., as taught in the prior art discussed above) solely to avoid adverse side effects such as polycythemia, renal vasoconstriction, hypertension and thromboembolism, as indicated for instance in the discussion found at col. 6, lines 45-61.

Further, as is evident from, for instance, col. 5, first 4 lines and/or col. 6, lines 58-65 the patentees obviously in general consider higher EPO dosages as being suitable to achieve the desired therapeutic effect, but chooses to utilize the lower disclosed dosages only to avoid the undesirable side effects. In contrast, the presently claimed method specifically utilizes low

concentration of EPO to achieve, specifically, a wound healing effect, i.e., an effect not seen with higher dosages.

Thus, the Westenfelder et al. reference first of all still teaches to use a considerably higher EPO dosage than that which is presently claimed by applicants. Secondly, the reference teaches to use such higher dosages for a different therapeutic indication, i.e., not for wound healing. Thirdly, the reference does not teach the use of a subpolycythemic dosage specifically to achieve a therapeutic purpose, i.e., it teaches to use such dosage only to avoid the occurrence of negative side effects.

To briefly summarize applicants' position in a non-limiting manner, applicants' argument against the 'obviousness' rejection of the claims entails, *inter alia*, a comparison of the EPO dosage levels recited for use in the presently claimed method, including the effect(s)s of such 'low dosage levels' on the body of a subject so treated, versus the significantly higher dosage ranges (and resultant significantly different physiological effects) disclosed in the case of the cited references. Notwithstanding, therefore, applicants' argument that the effects produced in the body of a subject by maintaining the EPO dosage level within the presently claimed range constitute not just a 'difference in degree', but also a difference in kind, the Examiner continues to hold that applicants' claimed EPO dosage level represent nothing more than the 'optimum or workable ranges' of this material which may be discovered, e.g., by routine experimentation.

To provide evidentiary support for the non-obviousness of the present claims, moreover, applicants submitted with their May 7, 2008 response filed in this case a Declaration Under 37 C.F.R. 1.132 from each of the named co-inventors which attempted to provide an analysis of the effects erythropoietin has on the healing of skin wounds in mice and to demonstrate to the Examiner, through the submission of experimental data, that the low dosage of EPO recited in the present claims represents a critical feature in achieving the aim of the claimed method, i.e., the healing of a wound in the skin of a subject. The Examiner, however, on p. 8 of the present Office Action, raised several objections to the data and how such data was presented in the subject declarations. Applicants have, thus, taken the Examiner's objections into account in presenting the data contained in the Second Declaration of Prof. Dr. Hermann Haller Under 37 C.F.R. §1.132 appended to this response. The Examiner is requested to consider the

experimental data provided in this 'second Haller' declaration and, based thereon, to reconsider and withdraw the §103 rejections of applicant's claims.

The appended 1.132 declaration of Prof. Dr. Haller (hereinafter, "the declaration") begins by describing the mechanism of wound healing and its various phases (see, e.g., ¶¶ 3-4). The declaration thereafter goes on to demonstrate, through the use of experimental evidence as detailed below, that in contrast to the high dosis levels of EPO taught for use in the prior art, e.g., in the references cited to reject applicants' claims, a systemic low dose application of EPO, i.e., at a level of 0.1 µg Aranesp®/kg of body weight/week (which is equivalent to 20 IU EPO/kg body weight/week), which is within the dosage level recited in the claims presently under examination of this application, serves to unexpectedly accelerate the Granulation Phase of wound healing. Prof. Dr. Haller uses an animal model of diabetes for his experiments since the analysis of skin lesions in this model is particularly reproducible and this system is therefore useful for testing potentially active pharmaceutical ingredients. This is important due to the fact that, as set forth in ¶5 of the declaration, accelerated granulation decreases the rate of wound infections, is associated with angiogenesis and reduces complications of wound healing.

As indicated in declaration ¶6, the experiments were carried out on groups of 10-12 week old male rats wherein each group was constituted of 38 rats. Wounds measuring 6 mm in circumference were placed, under anesthesia, on the backs of the animals on both sides of the spine. The animals were treated with one of a control/placebo (i.e., NaCl) or either a low-dose of EPO (according to the presently claimed method) or a high dose of the subject material, i.e., along the lines as taught in the cited prior art references combined to reject the claims of this application. The EPO was administered intravenously after wounding, and then again one week subsequent. Wound healing was assessed by planimetry and laser doppler analysis.

Taking into account the Examiner's comments in the present Office Action (p. 8) concerning a statistical analysis of the data contained in the prior declaration(s), the Exhibits provided with the present declaration display the data from the experiments as mean values and SEM. Furthermore, an unpaired t-test was used to test for significance wherein, in such test, a p-value of < 0.05 was considered to be significant.

With regard to the demonstration of the unexpectedly improved results obtained with EPO dosage values according to the present invention, declaration ¶7 states that Fig. A (Exhibit 7) demonstrates such an improvement in wound healing obtained during the Granulation Phase at day 3 and day 6. As stated therein, a comparison was made involving 4 groups of rats, i.e., (1) non-diabetic rats receiving a placebo; (2) diabetic rats receiving a placebo; (3) diabetic rats receiving a low dose of EPO; and (4) diabetic rats receiving a "prior art" 'high' dose of EPO. The results presented in Exhibit 7, "[c]learly demonstrate that the systemic low dosage application of EPO, as recited in the presently pending claims, significantly accelerates the Granulation Phase of the wound healing process."

Further to the above and as stated in declaration ¶8, a significant delay in the Granulation Phase was found to occur in diabetic animals compared to the non-diabetic placebo-receiving group of rats at day 3 after surgical wounding. The degree of wound healing in the diabetic rats was found, moreover, to be improved by treatment with EPO. The indicated paragraph then goes on to state that, as illustrated in Fig. B in Exhibit 8, an "impressive improvement" was obtained with the application of low-dose EPO whereas, in contrast, a significantly lower degree of improvement was found to occur in the case of the high-dose EPO group of animals at day 3. Once again, taking into account the Examiner's comments in the present Office Action with regard to the statistical analysis of the experimental data, the declaration states (in ¶8) that the healing process attributable to the low dose EPO treatment as illustrated in Fig. B of Exhibit 8 was normalized to the level of the non-diabetic animals.

In addition to the above, as shown in Fig. C (Exhibit 9), at Day 6 the wound healing in the low dose EPO group displays no significant difference when compared to the non-diabetic animals (Group 1). As stated in the indicated paragraph, the healing process was normalized to the level of the non-diabetic animals. Furthermore, the Exhibit additionally demonstrates that the high dose EPO group (Group 4) shows no significant difference when compared to the non-treated diabetic animals (Group 2), i.e., which received the placebo.

Thus, particularly from Exhibits 8 and 9 it is clear that the low dose EPO group shows, in the granulation period of wound healing, a level of wound healing which is, in particular at day 6, indistinguishable from the non-diabetic placebo treated control animals. In sharp contrast

thereto, neither at day 3 nor at day 6 did the high dose EPO treatment reach the degree of wound healing of the non-diabetic control animals. Instead the degree of wound healing was statistically indistinguishable from non-treated diabetic animals. Thus the treatment of wounded animals with low dose EPO leads to a statistically relevant improvement in wound healing, which is not only distinguishable from the high dose treatment by degree or by its extent, but is in fact a qualitative difference. This is due to the fact that the high dose treatment in the granulation phase of the wound healing process, which is a crucial process step in wound healing, has no statistically relevant effect at all.

The data presented in Prof. Dr. Haller's appended 1.132 declaration not only supports a statistically relevant effect of low dose EPO for closing wounds, it also leads to the conclusion that in the granulation phase the high dose EPO treatment has no effect at all, particularly in view of the error bars in Exhibits 7-9. In contrast, the low dose treatment clearly shows a statistically relevant effect that is indicated by a degree of closing which reaches, at day 6, the value for the control group of healthy animals.

In conclusion, therefore, the improved results achieved by the method recited in the pending application, as set forth in, e.g., Exhibits 7-9 of Prof. Dr. Haller's declaration, demonstrate the superiority in patients suffering from problems with wound healing of low-dose EPO treatment as recited in the claims presently under examination, versus the results obtained with a contrasting high-dose treatment along the lines disclosed in the references combined by the Examiner to reject applicants' claims.

The Examiner is, therefore, respectfully requested to reconsider and withdraw the rejection of applicants' claims under 35 U.S.C. §103.

Double Patenting Rejection

Further to the above, the Examiner also continues to maintain the *provisional* non-statutory obviousness-type double patenting rejection of claims 46, 52, 53, 59, 65, 70 and 90 over claims 4, 15-31and 35-44 of co-pending application Serial No. 10/586,896. The rejection is 'provisional' due to the fact that the conflicting claims have not, in fact, been patented.

In response to the double patenting rejection, applicants respectfully submit they believe that the evidence set forth in the appended declaration under 37 C.F.R. of Prof. Dr. Haller is sufficient to overcome the 'obviousness' rejection of the subject claims under 35 U.S.C. which, therefore, should be withdrawn. In that case, the double patenting rejection should be the only rejection remaining in the present application.

In such cases, as noted by applicants in their previous responses filed in this case, the M.P.E.P. indicates (see, e.g., §804 I B) that in the case of provisional obviousness-type double patenting rejections that are, as in the present instance, based on the claims of copending applications, "The 'provisional' double patenting rejection should continue to be made by the Examiner in each application as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in at least one of the applications." In the latter instance, i.e., wherein the provisional double patenting rejection remains as the only ground for rejection, the M.P.E.P. advises to withdraw the double patenting rejection and to make an 'actual' (i.e., not a provisional) rejection in the co-pending application based on the claims issuing from the present application.

The Examiner is, therefore, respectfully requested to also reconsider and withdraw the provisional double patenting rejection of applicants' claims presently under rejection.

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